FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER: O/98414 US

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/831954

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/09053	18-NOV-1999	20-NOV-1998

TITLE OF INVENTION: ESTROGENIC ESTRA-1,3,5(10)-TRIENES WITH DIFFERENTIAL EFFECTS ON THE...

APPLICANT(S) FOR DO/EO/US: LOOZEN, Hubert J.J. and SCHOONEN, Wilhelmus G.E.J.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [XX] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [XX] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [XX] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [XX] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [XX] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [XX] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [XX] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [ ] Other items or information:

EXPRESS MAIL EL400659227US

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/831954	PCT/EP99/09053	0/98414 US

21. [X] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	6 - 20 =		x **$18.00**	$	
Independent claims	1 - 3 =		x **$80.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$ 860.00	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$	
SUBTOTAL =				$ 860.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$ 860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 860.00	
				Amount to be refunded:	$
				charged:	$ 860.00

a. [ ] A check in the amount of $ _____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 02-2334 in the amount of $860.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [ ] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. _____. A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

William M. Blackstone
Akzo Nobel Patent Department
1300 Piccard Drive, Suite 206
Rockville, MD 20850
301-948-7400

SIGNATURE

William M. Blackstone
NAME

29,772
REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

LOOZEN, Hubert J. and SCHOONEN, Wilhelmus G.E.J.

Serial Number: To be assigned Group Art Unit: To be assigned

Filed: Concurrently herewith Examiner: To be assigned

For: ESTROGENIC ESTRA-1,3,5(120)-TRIENES WITH DIFFERENTIAL EFECTS ON THE ALPHA AND BETA ESTROGEN RECEPTRS, HAVING A LINEAR HYDROCARBON CHAIN OF FROM 5-9 CARBON ATOMS IN POSITION 11

Corresponding to: PCT/EP99/09053, filed November 18, 1999

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

May 15, 2001

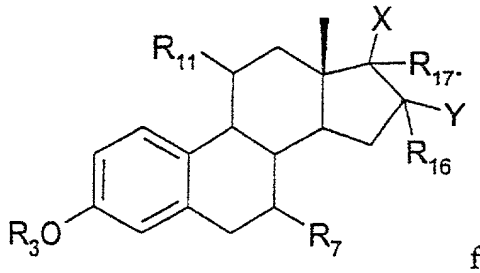
Sir:

Prior to the calculation of the fee in the above-identified application, please make the following amendments:

IN THE CLAIMS:

Please replace claims 1 - 5 with the following new claims 1 - 5.

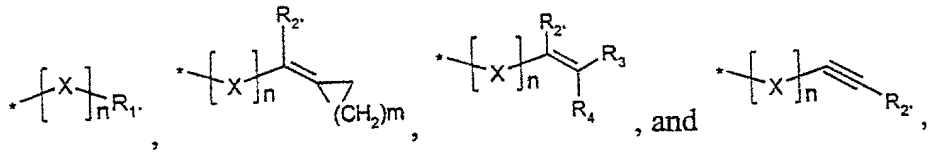
1. (amended) A steroid compound satisfying the following structural formula:



formula I

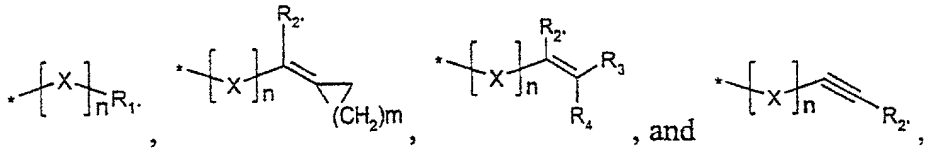
wherein:
one of X and Y is OH, the other being H;
R_3 is H or COR'_3, with R'_3 being alkyl or aryl;
R_7, R_{16}, and R_{17} each independently are H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl; R_{11} is a hydrocarbon group, which may be linear or branched, comprising one single linear chain having a length of from 5 to 9 carbon atoms as the longest chain on carbon atom no. 11 of the steroid skeleton, wherein said chain may be saturated or unsaturated.

2. (amended) A steroid compound according to claim 1, wherein R_{11} is selected from the following group of side-chain structures:



wherein X is CH_2, CH-alkyl or $C(alkyl)_2$, R_1 is H, aklkyl, C_3-C_7 cycloalkyl or together with X forms a C_3-C_7 ring system, R_2 is H, alkyl or C_3-C_7 cycloalkyl, R_3 and R_4 each independently are H, alkyl or C_3-C_7 cycloalkyl, unsubstituted or substituted with

2. (amended) A steroid compound according to claim 1, [characterised in that] wherein R_{11} is selected from the following group of side-chain structures:



wherein X is CH_2, CH-alkyl[,] or $C(alkyl)_2$, R_1 is H, aklkyl, C_3-C_7 cycloalkyl[,] or together with X forms a C_3-C_7 ring system, R_2 is H, alkyl[,] or C_3-C_7 cycloalkyl, R_3 and R_4 each independently are H, alkyl[,] or C_3-C_7 cycloalkyl [optionally], unsubstituted or substituted with halogen or CN, n is an integer of from 0-9, m is an integer of from 1-5.

3. (amended) A steroid compound according to claim 1, [characterised in that] wherein the longest chain in R_{11} comprises 5-7 carbon atoms.

4. (amended) A steroid compound according to claim 3, [characterised in that] wherein the longest chain in R_{11} comprises 5 carbon atoms.

5. (amended) A pharmaceutical composition comprising a steroid compound according to [any one of the preceding claims,] claim 1 and a pharmaceutically acceptable [auxiliaries] auxiliary.

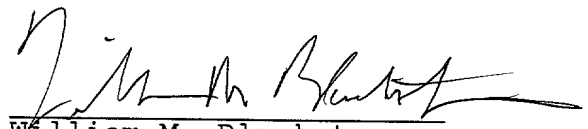
REMARKS

Claims 1 - 5 are amended, claim 6 is canceled, and claim 7 is added. Claims 1 - 5 and 7 are presented for examination.

The present amendments are made in order to correct grammatical errors and to conform the claim language to accepted U.S. PTO practice, and not for purposes of patentability under 35 USC 101, 102, 103 or 112, and no estoppel is created hereby.

It is believed that claims 1 - 5 and 7 recite a patentable improvement in the art. Favorable action is solicited. In the event any fees are required with this paper, please charge our Deposit Account No. 02-2334.

Respectfully submitted,



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Registration No. 29,772

Attorney's Docket No. O/98414 US

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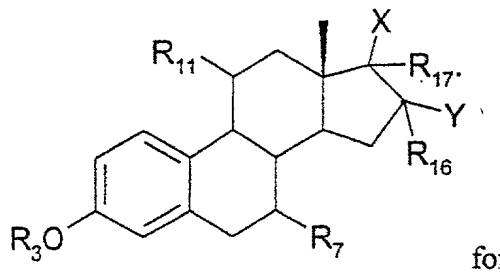
51LOOZEN-PRELIMINARY

VERSION W/MARKINGS TO SHOW CHANGES

1. (amended) A steroid compound satisfying the following structural formula:



formula I

wherein:

one of X and Y is OH, the other being H;

R_3 is H[,] or COR'_3, with R'_3 being alkyl or aryl;

R_7, R_{16}, and R_{17} each independently are H, alkyl, cycloalkyl, alkenyl, alkynyl[,] or aryl; R_{11} is a hydrocarbon group, which may be linear or branched, [provided that it comprises] comprising one single linear chain having a length of from 5 to 9 carbon atoms as the longest chain on carbon atom no. 11 of the steroid skeleton, wherein said chain may be saturated or unsaturated.

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original first and joint inventor (if plural names are listed below) of the subject matter for which a patent is sought on the invention entitled:

"Estrogenic estra -1,3,5(10)-trienes with differential effects on the alpha and beta estrogenreceptors, having a linear hydrocarbon chain of from 5-9 carbon atoms in position 11"

the specification of which
[CHECK ONE]
[ ]is attached hereto
[ ] was filed on _____ as Application Serial No. _____ and was amended on _____
[if applicable]

[X]as filed under the Patent Cooperation Treaty on **18/11/99**
Serial ***EP99/09053*** , The United States of America being designated.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined Title 37, Code of Federal Regulations Section 1.56(a)

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign applications(s) for patent or inventor's certificate having a filing date before that of the application(s) on which priority is claimed:

Prior Foreign Application(s)			Priority claimed
98203914.1	*EP*	*20/ 11 / 1998*	X Yes ___ No
Number	Country	Day/Month/Year filed	
_____	_____	_____	___ Yes ___ No
Number	Country	Day/Month/Year filed	
_____	_____	/ /	___ Yes ___ No
Number	Country	Day/Month/Year filed	

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose to the patent and Trademark

Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application.

(U.S. Serial No.) (Filing date) (Status-patented, pending, abandoned)

(U.S. Serial No. (Filing date) (Status-patented, pending, abandoned)

(2) And I hereby appoint as principal attorney, William M. Blackstone, Registration No. 29,772, and Michael G. Sullivan, Registration No. 35,377.

Please address all communications to:

William M. Blackstone
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Rockville, MD 20850-4373

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued theron.

Full name of sole or first inventor Loozen, H.J.J.

Hubert Jan Jozef

Inventor' signature _____ Date 2/5/2001

Citizenship Dutch

Residence and P.O. Address Meerhoek 602 5403 AC Uden NLX

The Netherlands

Full name of second joint inventor Schoonen W.G.E.J.

Wilhelmus Gerardus Eduardus Joseph

Inventor's signature _____ Date 2/5/2001

Citizenship Dutch

Residence and P.O.Address Parklaan 16 5345 BV Oss

The Netherlands NLX

Full name of third joint inventor _____

Inventor's signature _____ Date

Citizenship _____

ESTROGENIC COMPOUNDS

The invention is in the field of estrogenic compounds of the type based on the molecular structure of estradiol. I.e., compounds having a steroidal skeleton the A-ring of which is aromatic, and having a free or capped hydroxyl group at carbon atom No. 3 and at either of carbon atoms Nos. 16 or 17. Estrogenic compounds have a generally recognised utility in the treatment of estrogen-deficiency related disorders, such as menopausal complaints, osteoporosis, and in contraception.

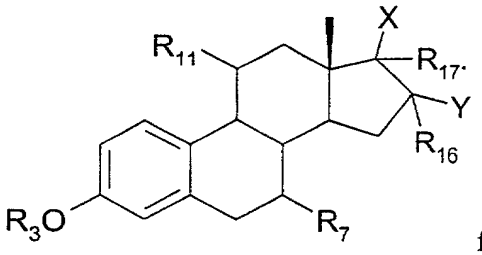
More precisely, the invention pertains to 11β-substituted estradiol derivatives. Such 11β-substituted estradiol derivatives are known from, *inter alia*, Napolitano et al. in J.Med.Chem. **1995**, *38*, 2774-2779 and Lobaccaro et al. in J.Med.Chem. **1997**, *40*, 2217-2227. From these documents, it can be learned that placing a substituent at the 11β-position may improve the binding affinity for the estrogen receptor, provided that said substituent is not too large. E.g., with an ethynyl group at C_{11} the binding increases, whereas with the next higher homologue, 1-propynyl, it is reported that the binding affinity undergoes a marked drop.

The state of the art in the field of estrogen receptor affinity discriminates between two estrogen receptors, denoted ERα and ERβ, see Mosselman et al., FEBS Letters 392 (1996) 49-53 as well as EP -A- 0 798 378. Since these receptors have a different distribution in human tissue, the finding of compounds which possess a selective affinity for either of the two is an important technical progress, making it possible to provide a more selective treatment of estrogen-deficiency related disorders, with a lower burden of estrogen-related side-effects.

The present invention is based on the unexpected finding that, despite the above teaching, certain 11β-substituted estradiol derivatives that deviate from those reported by Napolitano et al. possess a surprisingly higher estrogen receptor -affinity. Moreover, the present invention pertains to such 11β-substituted estradiol derivatives

as have a selective affinity for both the estrogen receptors ERα and ERβ. By way of preference, the present invention pertains to such 11β-estradiol derivatives as have a specific selective affinity in that these are agonists for ERα and antagonists for ERβ.

To this end, the invention resides in steroid compounds which satisfy the following structural formula I:



formula I

wherein:

one of X and Y is OH, the other being H;

R_3 is H, COR'$_3$ with R'$_3$ being alkyl* or aryl;

R_7, R_{16} , and R_{17} each independently are H, alkyl*, cycloalkyl*, alkenyl*, alkynyl*, aryl;

R_{11} is a hydrocarbon group which may be linear or branched, provided that it comprises one single linear chain having a length of from 5 to 9 carbon atoms as the longest chain on carbon atom no. 11 of the steroid skeleton, wherein said chain may be saturated or unsaturated;

It should be noted that carbon chain length of the groups denoted with an asterisk (*) is not particularly critical, but will generally be up to eight for the aliphatic and alicyclic groups, while aryl generally will be phenyl, pyridinyl, pyrimidyl, which groups can have substitutions customary in the art, such as alkoxy, hydroxy, halogen, nitro, cyano, and amino.

It should be noted that the exact structure of the estrogenic steroid skeleton is not critical as long as the regular requirements of an aromatic A-ring and hydroxyl groups on C_3 and C_{17} or C_{16} have been satisfied.

The present invention is directed to the 11β-substitution of such a steroid skeleton. It is the nature of the 11β substitution which has been found to lead to the unexpected effect on estrogen receptor affinity.

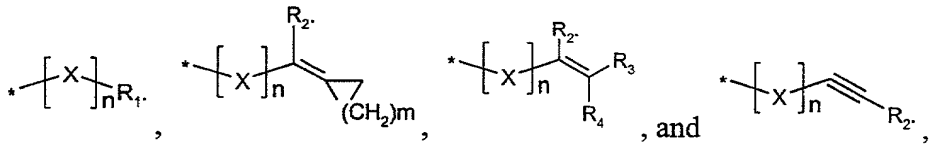
The mixed estrogen-receptor profile of the compounds according to the present invention, makes them suitable as improved estrogens, in the sense that they can be used in estrogen-related disorders, such as menopausal complaints and osteoporosis, and in contraception, and further may also be suitable in the treatment or prevention of Alzheimer's desease, breast tumor, benign prostate hypertrophy, and cardiovascular disorders. The preferred compounds of the invention, which have a marked ERα agonistic and ERβ antagonistic profile, are particularly suitable in the treatment and prevention of estrogen-deficiency related disorders under diminished estrogen-related side-effects. The strongly ERβ antagonistic compounds of the invention can also have a utility in the treatment and prevention of endometriosis and other estrogen-related disorders.

As indicated above, the 11β-substituent is a hydrocarbon group comprising a single linear chain having a length of from 5 to 9 carbon atoms. This means that either the main chain of the substituent has a length of from 5 to 9 carbon atoms and any branches have a shorter chain length, or a short group is directly attached to carbon no. 11 of the steroid skeleton as what would normally be regarded as the actual substituent, in which case a side-chain must be present in such a manner that the total number of carbon atoms present in the longest chain attached to carbon atom no. 11 of the steroid skeleton is 5-9.

(68)

The number of carbon atoms in the single longest chain according to the invention preferably is lower than 9. More preferably, the number of carbon atoms is 5-7 with 5 or 6 being most preferred. It is further preferred that the 11β-hydrocarbon chain is unbranched, and most preferably contains a double bond or a triple bond.

The 11β-substituent, i.e. R_{11} in formula 1 preferably is selected from the following group of side-chain structures:



wherein X is CH_2, CH-alkyl, or $C(alkyl)_2$, R_1 is H, alkyl, C_3-C_7 cycloalkyl, or together with X forms a C_3-C_7 ring system, R_2 is H, alkyl, or C_3-C_7 cycloalkyl, R_3 and R_4 each independently are H, alkyl, or C_3-C_7 cycloalkyl optionally substituted with halogen or CN, n is an integer of from 0-9, m is an integer of from 1-5.

It is preferred that the further substituent groups denoted in the description of formula I are the following groups:

alkyl is (1-8C) alkyl, meaning a branched or unbranched alkyl group having 1-8 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, hexyl and octyl;

cycloalkyl is (3-6C)cycloalkyl meaning a mono- or bicycloalkyl group having 3-6 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl:

alkenyl is (2-8C)alkenyl, meaning a branched or unbranched alkenyl group having 2 to 8 carbon atoms, such as ethenyl, 2-butenyl, etc.; preferably alkenyl is (3-7C) alkenyl;

alkynyl is (2-8C) alkynyl, which means a branched or unbranched alkynyl group having 2-8 carbon atoms, such as ethynyl and propynyl; preferably alkynyl is (3-7C) alkynyl;

The compounds of the invention may be produced by various methods known in the art of organic chemistry in general, and especially in the art of the chemistry of

steroids [see for example: Fried, J. and Edwards, J.A., *"Organic Reactions in Steroid Chemistry"*, Volumes I and II, Van Nostrand Reinhold Company, New York, 1972]. The synthesis of the 11β-substituted estradiol derivatives of the invention does not present any special problems to the person of ordinary skill in the art, as is is also evident from the examples given below. The compounds of the invention can also generally be synthesised analogously to the known 11β-substituted estradiol derivatives referred to above.

The present invention also relates to a pharmaceutical composition comprising the steroid compound according to the invention mixed with a pharmaceutically acceptable auxiliary, such as described in the standard reference Gennaro et al., Remmington's Pharmaceutical Sciences, (18th ed., Mack publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture.). The mixture of the steroid compounds according to the invention and the pharmaceutically acceptable auxiliary may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. nasal spray. For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants. polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. The steroid compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and any other preparation for sustained release.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

Furthermore, the invention relates to the use of the steroid compound according to the invention for the manufacture of a medicament in the treatment of estrogen-deficiency

related disorders such as peri- and/or post-menopausal complaints. Thus the invention also pertains to the medical indications of peri- and/or post-menopausal (climacteric) complaints and osteoporosis, i.e. a method of treatment in the field of HRT (hormone replacement therapy), comprising the administration to a patient, being a woman, of a compound as described hereinbefore (in a suitable pharmaceutical dosage form).

Further, the invention relates to the use of the steroid compound according to the invention in the manufacture of a medicament having contraceptive activity. Thus the invention also pertains to the medical indication of contraception, i.e. a method of contraception comprising the administration to a subject, being a woman or a female animal, of a progestogen and an estrogen as is customary in the field, wherein the estrogen is a compound as described hereinbefore (in a suitable pharmaceutical dosage form).

Finally the invention relates to the use of the steroid compound for the manufacture of a medicament having selective estrogenic activity, such a medicament being generally suitable in the area of HRT (hormone replacement therapy). .

The dosage amounts of the present steroids will be of the normal order for estradiol derivatives, e.g. of the order of 0.01 to 10 mg per administration.

The invention is further illustrated hereinafter with reference to some unlimitative Examples and the corresponding formula schemes referred to.

EXAMPLE 1

The synthesis of two compounds according to the invention, (10) and (11) in Scheme I is carried out as follows.

2

A mixture of 20 g of 11-butenylestrone **1**, 12 ml of ethyleneglycol, 20 ml of triethylorthoformate and 0.5 g of p-toluenesulfonic acid was heated for 2 h. Then the mixture was cooled and poured into sat.aq.$NaHCO_3$. The product was extracted into ethylacetate. After washing, drying and evaporation of the solvent, the crude product was treated with diisopropylether to afford 14 g of **2** as crystalline material; Mp184-185. R_f 0.58 (heptane/ethyl acetate 6/4).

3

To a solution of 0.5 g of **2** in 10 ml of THF was added 1 ml of dihydropyran, followed by 10 mg of p-toluenesulphonic acid. After stirring for 2 h the mixture was neutralized by addition of 0.5 g of $NaHCO_3$. The mixture was stirred for 15 min. and then poured into water and extracted with ethylacetate. Upon passing the product through a short silica column, 600 mg of **3** was obtained as an oil; R_f 0.75 (heptane/ethyl acetate 6/4).

4

To a solution of 600 mg of **3** in 10 ml of dry THF was added at 0°C 0.4 ml of 10M BH_3.dimethylsulfide complex. After stirring for 1 h all starting material had been consumed. The mixture was carefully treated with 1.6 ml of 10% NaOH and 1,2 ml of 30%aq. H_2O_2 . After stirring for 4 h the mixture was diluted with water and the product extracted into ethylacetate. Purification by column chromatography provided 470 mg of **4** as a viscous oil; R_f 0.27 (heptane/ethyl acetate 6/4).

5

To a suspension of 17 g of sodium acetate, 35 g of silica gel, and 17 g of pyridiniumchlorochromate in 150 ml of methylene chloride was added a solution of 9.5 g of alcohol **4** in 20 ml of methylenechloride. After stirring the mixture for 1 h, the oxidation was completed and 200 ml of ether and 50 g of Celite was added. The mass was stirred for 15 min and then filtered over a celite path . The residue was concentrated and passed through a short silica gel column, to provide 9,1 g of **5**; R_f 0.55 (heptane/ethyl acetate 6/4)

6

To a suspension of 1.3 g of isopropyltriphenylphosphonium bromide in 10 ml of dry THF was added at

- 30°C 2.2 ml of a 1.5 M solution of butyllithium in hexane. The mixture was stirred for 15 min. At -30° and for 0.5 h at O°. Then a solution of 0.47 g of aldehyde **5** in 2 ml of THF was added. After stirring for an additional 1 h at ambient temperature the reaction mixture was poured into water and extracted with ethyl acetate. Chromatography over silicagel, provided 450 mg of **6** as a colorless oil; R_f 0.70 (heptane/ethyl acetate 7/3); starting material R_f 0.46.

7

In a similar way as described above , the related cyclopropylidene derivative **6** was prepared from the aldehyde 5 and cyclopropyltriphenylphosphonium bromide .
R_f 0.65 (heptane/ethylacetate 7/3)

8

To a solution of 550 mg of **6** in 10 ml of acetone was added 2 ml of 2N HCl. The mixture was stirred for 1 hr. After neutralization with sat.aq. $NaHCO_3$ the mixture was diluted with water and the product was extracted with ethyl acetate. The material thus obtained was triturated with 70% ethanol, to provide 360 mg of **8** as a white solid ; Mp 190-191 °C; R_f 0.43 (heptane/ethyl acetate).

9

In a similar way as described for the related isopropylidene derivative **9** was prepared from the protected material 7 by treatment with 2N HCl; Mp 154-155 °C; R_f 0.38 (heptane/ethyl acetate 7/3).

10

To a solution of 350 mg of **8** in a mixture of 3 ml of THF and 1 ml of abs.ethanol was added 60 mg of sodium borohydride. After stirring for 1 hr excess hydride was destroyed by addition of acetone and after stirring for an additional ½ hr the mixture was diluted with water and the product extracted with ethyl acetate. The product thus obtained was triturated wth 60% ethanol, to provide 280 mg of **10**; Mp 205-207°C.

11

In an analogous way as described above , reduction of **9** with sodium borohydride afforded the required estradiol derivative **11**; Mp 178-179°C.

EXAMPLE II

The synthesis of two further compounds according to the invention, (18) and (21) in Scheme II is carried out as follows.

12

To a solution of 1 g of **3** in 20 ml of dioxane was added 2.8 ml of 2% OsO_4 in t-butanol. After stirring this mixture for 10 min. 4 ml of water and 3.4 g of $NaIO_4$ were added. After stirring for 1 h the reaction was complete . The mixture was poured onto water, and extracted with ethyl acetate. After chromatography of the crude product 0.5 g of aldehyde **12** was isolated as an oil; R_f 0.50 (heptane /ethyl acetate 6/4) 0.64 ; R_f **3** : 0.75.

13

A solution of 6.9 g of triphenylphosphine was added at -70° C to a solution of 4.38 g of tetrabromomethane in 30 ml of dichloromethane. . The mixture which had turned orange was stirred additionally for 15 min. at 0 °C, and then cooled again to -70°C. A solution of 3 g of steroid **12** in 10 ml of methylene chloride was added and the mixture was stirred for another 1.5 h. The reaction was then poured onto sat.aq. $NaHCO_3$ solution and extracted with dichloromethane. The product thus isolated was purified by chromatography to provide 1.39 g of **13**; Mp 163-164°C (ethanol/water).

14

To a solution of 870 mg of **13** in 10 ml of acetone was added 1.6 ml of 1 N HCl. The mixture was stirred for 2 h. Then the reaction was neutralized by addition of $NaHCO_3$ followed by dilution with 50 ml of water. The product was extracted into ethyl acetate. After drying and concentration 0.70 g of **14** were obtained ; R_f 0.60 (heptane/ethyl acetate 6/4).

15

To a solution of 3.7 g of **14** in 20 ml of methanol and 20 ml of THF was added 500 mg of sodiumborohydride. After stirring for 1 h the mixture was poured into 250 ml of sat.aq.NH_4Cl solution and extracted with ethyl acetate. After drying and concentration of the organic phase, the residue was crystallized from ether, to provide 2.7 g of **15** ; Mp 142-144°C, R_f 0.45 (heptane/ethyl acetate 6/4).

16

To a solution of 2 g of **15** in 40 ml of THF was added 6 ml of dihydropyran, followed by 45 mg of p-toluenesulphonic acid. After stirring for 1½ h the reaction mixture was poured into 200 ml of sat.aq. $NaHCO_3$ solution , and the product was extracted into ethyl acetate, to provide 2,9 g of **16** as an oil; R_f 0.78 (hexane/ethylacetate 6/4)

17

To a solution of 2.9 g of **16** in 50 ml of dry THF was added at -78 °C 6 ml of 1.6M BuLi (in hexane) solution. The mixture was stirred for 30 min. at this temperature . Then 1.4 ml of methyliodide was added and the reaction was allowed to stir for 3 h at -15°C , followed by 3 h at room temperature. After pouring the mixture in 250 ml of water the product was extracted into ethyl acetate, and purification was performed by chromatography over silica gel, to provide 1.4 g of **17** as an oil; R_f 0.38 (heptane/acetone 95/5); R_f0.71 (heptane/ethylacetate 6/4, starting material Rf 0.78).

18

To a solution of 1.35 g of **17** in 30 ml of a 1/1 mixture of methanol/THF was added 100 mg of p-toluenesulfonic acid. After stirring for ½ h the mixture was poured into 100 ml of sat. aq. $NaHCO_3$ solution and the product was extracted into ethyl acetate. After chromatographic purification 510 mg of **18** was obtained as a white solid; Mp 180-182°C, R_f 0.35 (heptane/ethylacetate 6/4).

19

To a suspension of 2.2 g of cyclopropyltriphenylphosphonium bromide (previously dried over P_2O_5 in vacuo at 80°C) in 30 ml of THF was added at -10°C 3.2 ml of a 1.6 M BuLi in hexane solution. After stirring for 1 hr at 0°C, a solution of 1.2 g of **12** in 5 ml of THF was added . The mixture was stirred for 1 h at room temperature and then poured into water. Extraction with ethylacetate, followed by chromatography , provided 0.93 g of **19** as an oil; R_f 0.73 (heptane/ethyl acetate 7/3).

20

Deprotection of the ketal and tetrahydropyranyl ether was achieved by stirring 0.45 g of **19** in 10 ml of methanol in the presence of 50 mg of p-toluenesulphonic acid for 2 hr. The reaction mixture was poured into 5% aq $NaHCO_3$ solution and the product

was extracted with ethyl acetate. Chromatography provided 120 mg of pure **20**; R_f 0.27 (heptane/ethyl acetate 7/3).

21

Reduction of the 17-keto group was achieved by treatment of a solution of 360 mg of **20** in a mixture of 5 ml of methanol and 5 ml of THF with 80 mg of sodium borohydride. After stirring for 2 h the mixture was poured into 30 ml of sat.aq. NH_4Cl solution and the product was extracted with ethyl acetate.. Chromatography, followed by trituration with heptane provided 230 mg of **21** as a white solid; Mp 178-179 °C. R_f 0.44 (heptane/ethylacetate 6/4).

EXAMPLE III

The compounds of Examples I and II, as well as several other compounds (synthesized in analogous manner) are tested for their estrogenic and anti-estrogenic activity.

Test medium: Intact recombinant CHO cells stably co-transfected with the rat oxytocin promoter and the luciferase reporter gene and either the human estrogen receptor β or the human estrogen receptor α. Both cell lines have been produced within the Department of Biotechnology and Biochemistry (BBC) (N.V. Organon) and are known under the name CHO-ERRO 2B1-1E9 for CHO-ERα and CHO-ERβ RO LUC for CHO-ERβ.

The estrogenic activity of compounds is determined in an in vitro bioassay (CHO-ER α) with recombinant Chinese hamster ovary (CHO) cells stably co-transfected with the human estrogen α (hERα), the rat oxytocin promoter (RO) and the luciferase reporter gene (LUC). The estrogenic activity (potency ratio) of a test compound to promote the transactivation of the enzyme luciferase mediated via the estrogen

receptor α is compared with the standard estrogen Org 2317 (estradiol 1,3,5 (10)-estratriene-3,17β-diol). The estrogenic activity (potency ratio) of a test compound to promote the transactivation of the enzyme luciferase mediated via the estrogen receptor β is determined in the same fashion but using recombinant Chinese hamster ovary (CHO) cells stably co-transfected with the human estrogen β (hERβ) (bioassay CHO-ERβ).

The anti-estrogenic activity of compounds is determined in the same bioassays (CHO-ERα and CHO-ERβ), but now the anti-ERα and anti-ERβ activity (potency ratio) of a test compound to inhibit the transactivation of the enzyme luciferase mediated via ER α or ERβ by Org 2317 (estradiol 1,3,5 (10)-estratriene-3,17β-diol) is measured.

The results are presented in the Table below. A rating of the compounds is given in which (-) means that it does not satisfy the ER affinity profile of the present invention, while (+) means a compound according to the invention, i.e. an agonist for ERα and an antagonist for ERβ.

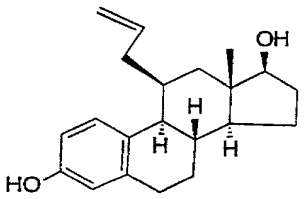
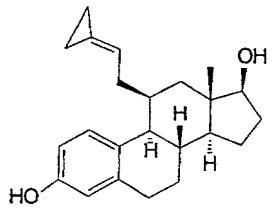
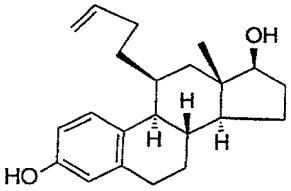
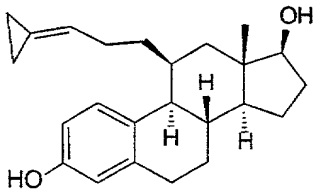
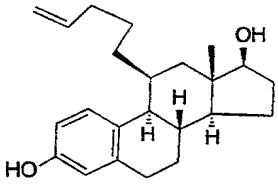
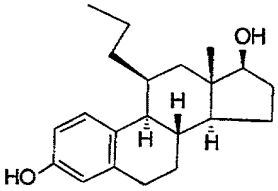
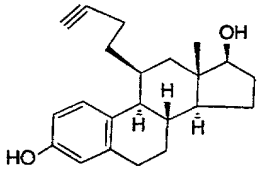
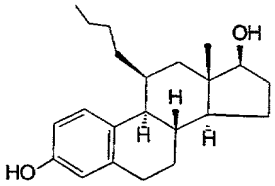
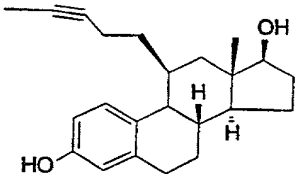
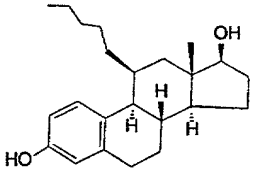
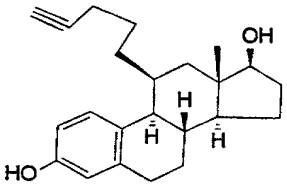
68

Table A

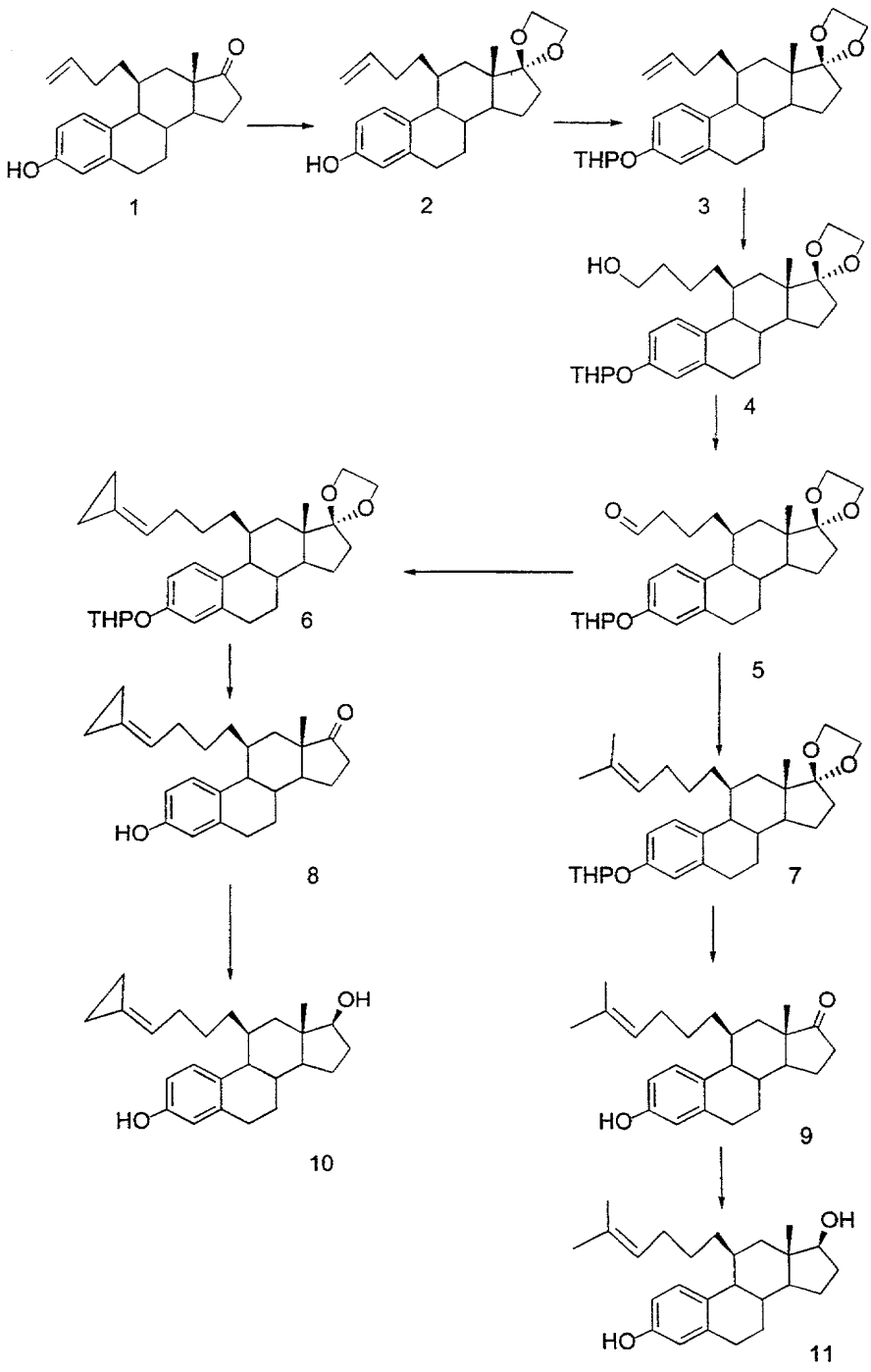
Compound	ER-α	ER-β	Rating
1	agonist	agonist	-
2	agonist	agonist	-
3	agonist	antagonist	+
4	agonist	agonist	-
5	agonist	antagonist	+
6	agonist	antagonist	+
7	agonist	agonist	-
8	agonist	antagonist	+
9	agonist	agonist	-
10	agonist	agonist	-
11	agonist	antagonist	+

(68)

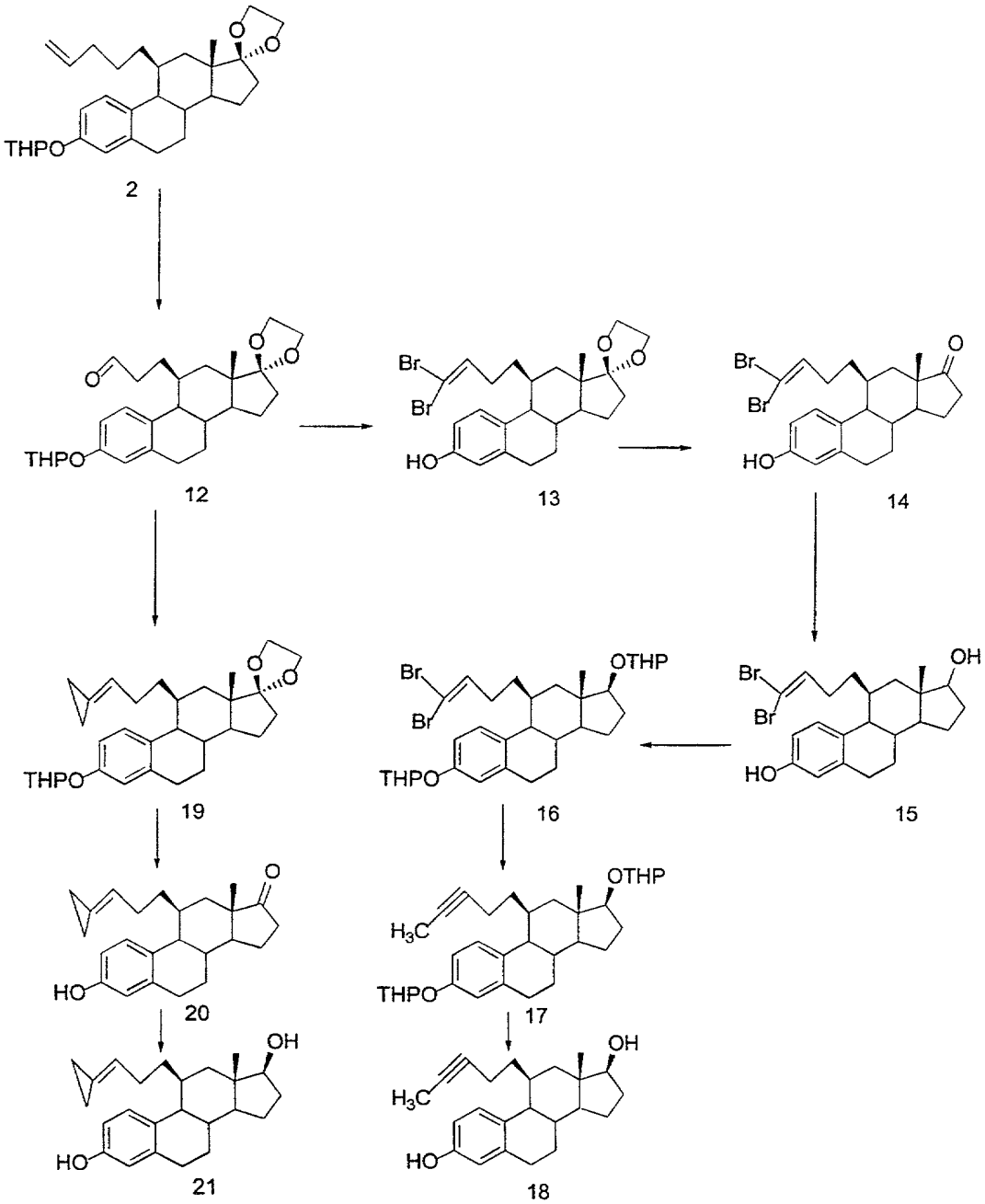
Table B

 (1)	 (7)
 (2)	 (8)
 (3)	 (9)
 (4)	 (10)
 (5)	 (11)
 (6)	

Scheme I

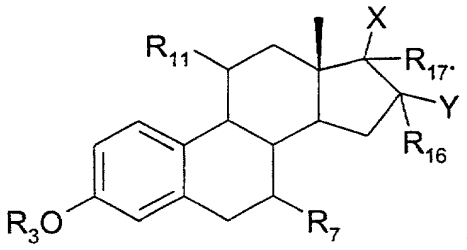


Scheme II


THPO
2
THPO
12
Br
Br
HO
13
Br
Br
O
HO
14
THPO
19
Br
Br
OTHP
THPO
16
Br
Br
OH
HO
15
HO
20
O
H3C
OTHP
THPO
17
HO
21
OH
H3C
OH
HO
18

Claims:

1. A steroid compound satisfying the following structural formula:



formula I

wherein:

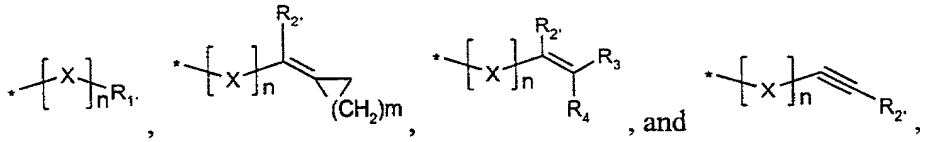
one of X and Y is OH, the other being H;

R_3 is H, COR'$_3$ with R'$_3$ being alkyl or aryl;

R_7, R_{16}, and R_{17} each indepenently are H, alkyl, cycloalkyl, alkenyl, alkynyl, aryl;

R_{11} is a hydrocarbon group which may be linear or branched, provided that it comprises one single linear chain having a length of from 5 to 9 carbon atoms as the longest chain on carbon atom no. 11 of the steroid skeleton, wherein said chain may be saturated or unsaturated.

2. A steroid compound according to claim 1, characterised in that R_{11} is selected from the following group of side-chain structures:



wherein X is CH_2, CH-alkyl, or C(alkyl)$_2$, R_1 is H, alkyl, C_3-C_7 cycloalkyl, or together with X forms a C_3-C_7 ring system, R_2 is H, alkyl, or C_3-C_7 cycloalkyl, R_3 and R_4 each independently are H, alkyl, or C_3-C_7 cycloalkyl optionally substituted with halogen or CN, n is an integer of from 0-9, m is an integer of from 1-5.

3. A steroid compound according to claim 1, characterised in that the longest chain in R_{11} comprises 5-7 carbon atoms.

4. A steroid compound according to claim 3, characterised in that the longest chain in R_{11} comprises 5 carbon atoms.

5. A pharmaceutical composition comprising a steroid compound according to any one of the preceding claims, and pharmaceutically acceptable auxiliaries.

6. The use of a steroid compound according to any one of claims 1-4 for the manufacture of a medicine in the treatment of estrogen-deficiency dependent disorders.